McLaren HEALTH CARE		Policy Title:	Expanded Access of Investigational Drugs and Devices
Effective Date:	November 3, 2017	**Policy Number:**	MHC_RP0127
Review Date:	August 17, 2020	**Section:**	Research Integrity
Revised Date:	January 18, 2023	**Oversight Level:**	Corporate
Administrative Responsibility:	Corporate Manager of Research Integrity Institutional Official, HRPP		

1. Purpose

1.1. To describe the procedures for utilizing the Food and Drug Administration (FDA) Expanded Access Program (EAP) including individual patient and intermediate or large population treatment investigational new drug (IND) applications.

2. Scope

2.1. This policy and procedure applies to all research at McLaren Health Care and its subsidiaries that involve the use of a non-approved, investigational use of an approved marketed product in a clinical protocol.

3. Definitions

3.1. Refer to Appendix I *"Definitions"*

4. Policy

4.1. The terms emergency use and compassionate use are not synonymous, according to federal regulations. Investigators must be aware of the specific standards for emergency use and compassionate use in order to avoid violating federal regulations. For the purpose of this policy the term "expanded access" and "compassionate" will be used interchangeably.

4.2. Clinical trials using investigational drugs and biologics and devices on human participants are performed under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) unless the trial/use qualifies for an FDA exemption. These clinical trials must be approved by the FDA and by MHC IRB prior to the onset of the study.

4.3. The FDA will permit an investigational product to be used under the Expanded Use Program (EAP) for the treatment of a serious or life-threatening disease or condition when all the following apply:

4.3.1. There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

4.3.2. Patient enrollment in a clinical trial is not possible;

4.3.3. Potential patient benefit justifies the potential risks of treatment; and

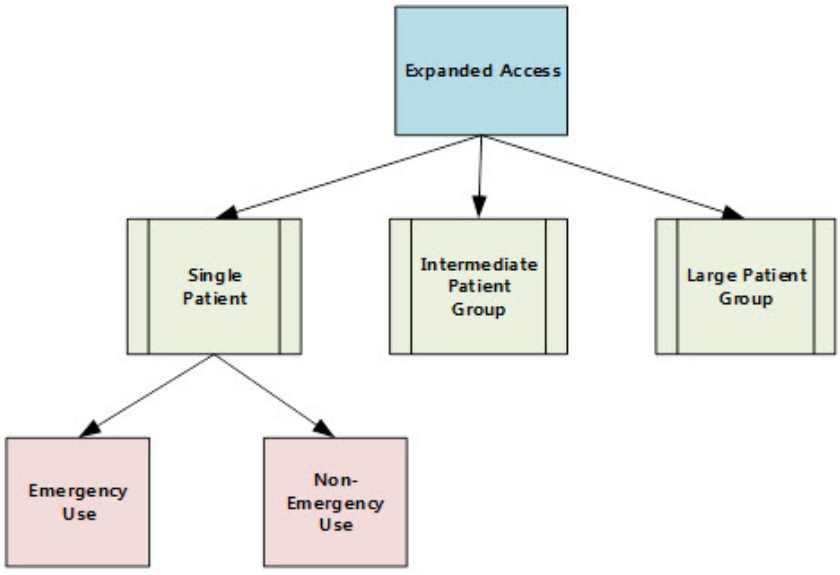
4.3.4. Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

4.4. An option for treating patients with an unapproved test article outside of a clinical trial is the Expanded Access Program. The IRB must prospectively approve Expanded Access requests.

4.5. While the primary purpose of expanded access is treatment, not research, FDA submission and IRB review are required.

4.6. The requirements and categories of expanded access for investigational drugs and devices are similar but not identical. Expanded access to biologics is typically via the expanded access pathways available for drugs unless the biologic is classified as a medical device.

4.6.1. Drugs - The FDA describes three distinct categories of EAP based on the number of people who need access and the level of risk. An expanded access IND submission to the FDA is required for each type of expanded access.



1. Single (Individual) Patient Expanded Access: Including emergency use IND (21 CFR 312.310) commonly held by the treating physician or investigator for treatment of an individual patient (referred to as a single patient IND) unless a sponsor agrees to make a drug for which they hold an IND available under their IND (referred to as a single patient protocol).

2. Intermediate-Size Patient Population Access: Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol) to an investigational drug or to an approved drug that is not available through marketing channels because, for example, the drug is in shortage or isn't marketed because of conditions associated with its approval. —The sponsor of the existing IND is responsible for submitting an intermediate-size patient population protocol for expanded access to the FDA under their IND.

3. Large population or Widespread Access: Expanded access for widespread treatment use through a *treatment IND or treatment protocol* (designed for use in larger patient populations) (21 CFR 312.320).

4.6.2. Devices – Similar to drugs, FDA provides three categories of expanded access to unapproved or uncleared medical devices:

4.6.2.1. Emergency Use – for when an individual patient is in a life-threatening situation and needs immediate treatment, there are no satisfactory alternative options, and there is no time to get FDA approval for the use. Procedures for single patient emergency use when there is not time to obtain IRB approval are described in MHC_RP0119 "Emergency Single Use of an Unapproved Drug, Biologic or Device".

4.6.2.2. Compassionate Use – for when a single patient, or small group of patients, has a life-threatening or serious disease or condition, there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and the potential patient benefit justifies the potential risks of the investigational device. FDA and IRB approval are required prior to use.

4.6.2.3. Treatment IDE – when the data for a device in an existing trial supports that the device is effective, access to the device may be made available to additional patients with life-threatening or serious diseases under a treatment IDE. Criteria for Treatment IDEs to be approved by the FDA include: (1) the device is intended to treat or diagnose a serious or immediately life-threatening disease or condition, (2) there is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population, (3) the device is under investigation in a clinical trial for the same use under an approved IDE, or all clinical trials have been completed, and (4) the sponsor of the clinical trial is pursuing marketing approval or clearance of the device with due diligence. FDA and IRB approval are required prior to use.

4.7. When FDA approval of an IND or IDE is required, the IRB will not finalize approval of an application for expanded access use until the IND or IDE has been approved by the FDA. Expanded access requires prospective review by the IRB and informed consent/authorization from the patient or Legally Authorized Representative (LAR).

5. Procedure

Expanded Access to Investigational Drugs and Biologics

5.1. Single Patient Emergency Use – See MHC_RP0119 Emergency Use for Single Use

5.2. Single (Individual) Patient IND, Non-Emergency

Criteria for Use

5.2.1. The physician or PI will evaluate the individual patient expanded access requirement:

5.2.1.1. Evaluate the potential risks and benefits

5.2.1.2. Confirm that the patient meets the following criteria:

5.2.1.2.1. The patient has a **serious or immediately life-threatening disease or condition** as defined by the FDA:

5.2.1.2.2. There is no available comparable or satisfactory alternative therapy available for the patient

5.2.1.2.3. There are no available clinical trials for the patient (e.g., because of a lack of open trials, because the patient is ineligible, because of the location of the trials, etc.)

Confirm with the Sponsor and FDA

5.2.1. Confirm the manufacturer or sponsor will provide the drug/biologic for the patient and, if so, whether they will be the sponsor (by adding the patient on to an existing IND) or you will need to serve as such and submit the request to the FDA.

5.2.2. Before submitting an individual patient IND to the FDA, a physician or PI must confirm that the manufacturer will provide the drug. If a manufacturer has an existing EAP IND available, the PI may be able to coordinate access to the drug through the manufacturer's approved IND rather than filing a separate individual patient IND.

5.2.2.1. FDA developed Form 3926 specifically for physicians requesting an expanded access IND for an individual patient. *The form includes an option to request FDA waive the requirement review by the convened IRB, permitting expedited review.*

5.2.2.2. If you will be the sponsor:

5.2.2.2.1. Obtain a Letter of Authorization (LOA) from the manufacturer and, if available, a sample treatment protocol and/or informed consent form (if the

manufacturer does not have one, use the McLaren ICF template found on the Research Integrity website).

5.2.2.2.2. Find out if the manufacturer will provide the drug/biologic free of charge and, if not, what the cost will be.

5.2.2.2.3. Submit the expanded access request to the FDA following their instructions for either a Non-Emergency or Emergency Individual Patient IND. When using Form FDA 3926 (preferred method), be sure to check the 10.b. box for Alternative IRB Review Procedures (this permits review by the IRB Chair instead of the convened IRB). In an emergency, FDA may authorize the use via phone, fax, or email with a requirement to submit the application and LOA within 15 business days.

IRB review and approval are required

5.2.2.3. PI will submit:

5.2.2.3.1. Expanded Access application in the IRB electronic application system.

5.2.2.3.2. A copy of the FDA Form 3926 (for individual patient requests).

5.2.2.3.3. An individual patient IND approval letter (or other form of documentation) from the FDA; an investigator's brochure, if applicable.

5.2.2.3.4. a description of patient situation details of the patient's history, diagnosis, summary/response to prior therapy, comorbidities, and concomitant medications.

5.2.2.3.5. a treatment plan adequate to assess whether risks have been minimized and are reasonable in relation to anticipated benefits and

5.2.2.3.6. a copy of the informed consent/authorization form which includes the statement indicating that although the primary use of the drug is for treatment, the drug is investigational, and FDA has not determined it is safe or effective for the condition of treatment.

5.2.3. IRB staff screen the IRB submission and verify completeness.

5.2.4. If the IND was requested using the Form 1571 or the waiver option on Form 3926 was not checked, the IRB office staff will schedule the submission for convened review as outlined in the policy MHC_RP0107 Initial Review of Human Subject Research.

5.2.5. If the IND was requested using Form 3926 and the waiver option was checked, the IRB office staff send for review by the IRB Chair or designee as outlined in the policy MHC_RP0107 Initial Review of Human Subject Research.

5.2.6. Treatment may begin as soon as FDA and IRB approval have been obtained.

PI Reporting Requirements

5.2.7. The physician or PI must comply with FDA's reporting requirements including reporting a written summary of the results of the expanded access use to the IND sponsor or the FDA, safety reports, and annual reports when the treatment continues for 1 year or longer. The IRB should be provided with a copy of all such reports. The PI is also required to report any unanticipated problems, noncompliance, or other issues to the IRB as outlined in MHC policies and procedures for research..

5.3. Expanded Access for Intermediate-Size Patient Population and Treatment IND

Intermediate-Size Patient Population Access is available for use when it is expected that the product will be needed for more than one patient but generally fewer patients than a Treatment IND or Protocol (which are intended for widespread access).

Criteria for Use

5.4. The FDA and the investigating physician must determine that the 3 criteria listed above in the **Single (Individual) Patient IND** section are met. Additionally, these criteria must be met:

5.4.1. There is enough evidence that the investigational drug or biologic is safe at the dose & duration proposed for expanded access use to justify a clinical trial of the investigational drug or biologic in the approximate number of patients expected to receive the drug under expanded access; AND

5.4.2. There is at least preliminary clinical evidence of effectiveness of the investigational drug or biologic, or of a plausible pharmacologic effect of the investigational drug or biologic to make expanded access use a reasonable therapeutic option in the anticipated patient population.

Use of this mechanism improves efficiency by reducing duplicative reviews. There are two pathways for intermediate-size patient populations available under FDA regulations:

5.4.3. Intermediate-Size Patient Population Expanded Access INDs

5.4.3.1. Submitted to FDA as a new IND by either a sponsor or a sponsor-investigator.

5.4.3.2. Unless FDA notifies the sponsor otherwise, there is a 30-day waiting period before treatment may begin.

FDA approval is required

5.4.4. Intermediate-Size Patient Population Expanded Access Protocols

5.4.4.1. Submitted to FDA as an addendum protocol to an existing IND by the sponsor of the existing IND.

5.4.4.2. May also be used to allow access to treatment with an approved drug that is not available through marketing channels (e.g., because of restrictions on use or because of a drug shortage).

5.4.4.3. No 30-day waiting period, but the protocol must be received by the FDA and approved by the IRB before treatment can begin.

IRB review and approval are required

5.4.5. Intermediate-Size Patient Population Expanded Access INDs and Protocols must be reviewed and approved by the convened IRB, alternative review by the IRB Chair is not allowed under FDA regulations for these pathways.

5.4.6. Please contact the HRPP/IRB office at 248-484-4950 when contemplating an Intermediate-Size Patient Population Access protocol so we can facilitate the process. If the IND or Protocol has already been approved by another IRB, IRB Reliance may be possible.

5.4.7. The PI follows procedures described in the policy MHC_RP0107 Initial Review of Human Subject Research with the following additions and provisions:

5.4.7.1. Inclusion of the phrase "TREATMENT IND" in the title.

5.4.7.2. Documentation of FDA treatment IND approval (i.e., correspondence from the FDA or commercial sponsor, IND number printed on sponsor protocol); and

5.4.7.3. Related materials including the treatment protocol, investigator's brochure, informed consent/authorization form, and potential investigational drug costs.

5.4.8. IRB office staff screen the IRB submission following procedures described in the policy MHC_RP0107 Initial Review of Human Subject Research

5.4.9. The convened IRB reviews the protocol as outlined in the policy MHC_RP0107 Initial Review of Human Subject Research and according to federal regulations.

FDA follow-up is required

The Sponsor and PI must comply with FDA's reporting requirements. The IRB should be provided with a copy of all reports the PI submits to the sponsor and/or FDA (when the PI is the Sponsor). The PI is also required to report any unanticipated problems, noncompliance, or other issues to the IRB as outlined in MHC policies and procedures for research.

5.5. Expanded Access for Large Patient Population (Treatment IND and Treatment Protocol)

5.5.1. Expanded Access Treatment INDs and Protocols are available when widespread use of an investigational drug is anticipated.

Criteria for Use and FDA approval

5.5.2. Unlike the other expanded access pathways, additional criteria apply, including that the investigational product must be under active development for marketing. A 30-day waiting period applies after application to the FDA before treatment can begin, unless the FDA notifies the sponsor that treatment may begin earlier.

5.5.3. The FDA and the physician must determine that the 3 criteria listed above in the overview section are met. Additionally, the FDA and the physician must determine that the following criteria are met:

Trial status:

5.5.3.1. The drug or biologic is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, OR

5.5.3.2. All clinical trials of the investigational drug or biologic have been completed; AND

Marketing status:

5.5.3.3. The sponsor is actively pursuing marketing approval of the investigational drug or biologic for the expanded access use with due diligence; AND

Evidence:

5.5.3.4. When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; OR

5.5.3.5. When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials but could be based on more preliminary clinical evidence.

5.5.3.6. Treatment INDs are submitted as a protocol under a new IND. Treatment INDs may be submitted by either industry sponsors or sponsor-investigators (but this is unusual).

5.5.3.7. Treatment Protocols are submitted as a protocol to an existing IND by the sponsor of the existing IND. This path is preferred because having all of

data under a single IND facilitates the identification of safety concerns and the product review process.

IRB review and approval are required

5.5.4. Prospective IRB review and approval are required. Submit an Application form plus FDA approval letter, sponsor acknowledgement letter, and consent with HIPAA authorization to the IRB. The IRB must ensure that the FDA granted approval before the expanded access use at MHC may be approved by the IRB. IRB.

Follow-up is required

5.5.5. Submit to the sponsor or FDA (if the PI is the sponsor) all IND safety reports promptly, annual reports if the protocol continues for one year or longer, and any other FDA or Sponsor-required reports. The PI is also required to report any unanticipated problems, noncompliance, or other issues to the IRB as outlined in MHC policies and procedures for research.

5.5.6. The sponsor (or sponsor/investigator) is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

5.5.7. Treatment IND or Treatment Protocol: A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments.

5.5.7.1. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

5.5.7.2. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks.

5.5.7.3. Prospective IRB review and approval is required. Alternative review by the IRB Chair is not allowed under FDA regulations for these pathways.

5.5.7.4. All of the following requirements must be met before a treatment IND can be issued:

5.5.7.4.1. The drug is intended to treat a serious or immediately life-threatening disease;

5.5.7.4.2. There is no satisfactory alternative treatment available;

5.5.7.4.3. The drug is already under investigation or trials have been completed;

5.5.7.4.4. The trial sponsor is actively pursuing marketing approval.

5.5.7.4.5. The FDA identifies two special considerations when a patient is to be treated under a treatment IND:

5.5.7.4.5.1. Informed Consent. Informed consent is especially important in treatment use situations. The subjects are desperately ill and will be receiving medications which have not been proven either safe or effective in a clinical setting, making them particularly vulnerable. Both the setting and their desperation may work against their ability to make an informed

assessment of the risk involved. Therefore, the IRB should ensure potential subjects are fully aware of the risks involved in participation.

5.5.7.4.5.2. Charging for Treatment INDs. The FDA permits charging for a drug, agent, or biologic used in a treatment IND. When subjects will be expected to pay such costs, the IRB should be particularly mindful, as this may preclude economically disadvantaged persons from receiving access to these test articles. The IRB should balance this interest against the possibility that, the drug will not be available for treatment use until it receives full FDA approval, unless the sponsor can charge for it.

5.6. Expanded Access of Investigational Devices

5.6.1. Compassionate Use – for when a single patient, or small group of patients, has a life-threatening or serious disease or condition, there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and the potential patient benefit justifies the potential risks of the investigational device. FDA and IRB approval are required prior to use.

5.6.2. Responsibilities

5.6.2.1. Investigator and/or Physician:

5.6.2.1.1. Request authorization to obtain the investigational device from the device manufacturer. The manufacturer may agree or disagree. If the manufacturer disagrees, the physician cannot use the device under the compassionate use pathway.

5.6.2.1.2. Obtain FDA's approval for the "compassionate use". If there is an IDE for the device, the IDE sponsor submits an IDE supplement to the FDA requesting approval for compassionate use. If there is no IDE for the device, the physician or manufacturer submits a compassionate use request to the FDA, along with a description of the device provided by the manufacturer. Instructions for compassionate use submissions are provided on FDA's "Expanded Access for Medical Devices" website.

5.6.2.1.3. Devise a schedule for patient monitoring, taking into consideration the investigational nature of the device, to address the specific needs of the patient, and to detect any possible problems with the use of the device.

5.6.2.1.4. Obtain clearance from the McLaren hospital officials.

5.6.2.1.5. Obtain an independent assessment from an uninvolved physician.

5.6.2.1.6. Submit the "Expanded Use Application" Submission Form with its supporting documentation and obtain the IRB Chairperson's or Vice Chairperson's concurrence.

5.6.2.1.7. Obtain informed consent from the patient using an IRB-approved consent form.

5.6.2.1.8. Report any problems from the use of the device to the IRB and the sponsor as soon as possible.

5.6.2.1.9. A follow-up report should be submitted to the FDA by whoever submitted the compassionate use request (the IDE sponsor, the manufacturer, or the physician) within 45 days of using the investigational device. The report should include summary information regarding patient outcome. If any problems occurred as a result of the use of the device, these should be reported to the IRB as soon as possible and included in the follow-up report. A copy of the follow-up report should be submitted to the IRB.

5.6.2.2. IRB Chair or designees:

5.6.2.2.1. Determine that the proposed use is not research supported and regulated by DHHS.

5.6.2.2.2. The IRB Chairperson or Vice-chairperson shall determine whether they concur with the compassionate use request and that it fulfills all of the following FDA criteria as outlined on FDA's "Expanded Access for Medical Devices" website.

5.6.2.2.3. In the event that the plan as outlined by the investigator does not comply with the FDA regulations and guidance, the IRB chair or designee will provide information to the investigator on how to comply with the regulations and guidance.

5.6.2.2.4. The IRB must:

5.6.2.2.4.1. Document concurrence of the IRB Chairperson or Vice-chairperson

5.6.2.2.4.2. Ensure FDA approval for the compassionate use

5.6.2.2.4.3. Review and approve the informed consent document prior to use

5.6.2.2.4.4. Receive reports of any problems with the use

5.6.2.2.4.5. Receive follow-up reports after the use

5.6.3. Treatment IDE – when the data for a device in an existing trial supports that the device is effective, access to the device may be made available to additional patients with life-threatening or serious diseases under a treatment IDE. Criteria for Treatment IDEs to be approved by the FDA include: (1) the device is intended to treat or diagnose a serious or immediately life-threatening disease or condition,

(2) there is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population, (3) the device is under investigation in a clinical trial for the same use under an approved IDE, or all clinical trials have been completed, and (4) the sponsor of the clinical trial is pursuing marketing approval or clearance of the device with due diligence. FDA and IRB approval are required prior to use.

5.6.3.1. Responsibilities:

5.6.3.1.1. The IDE Sponsor is responsible for obtaining approval for a Treatment IDE from the FDA, for complying with all applicable responsibilities under 21 CFR 812, for ensuring IRB approval is obtained in accordance with 21 CFR 56, and informed consent is obtained in accordance with 21 CFR 50.

5.6.3.1.2. A physician who receives an investigational device for treatment use under a treatment IDE is an investigator under the IDE and is responsible to meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56. IRB approval must be obtained before use of the device via submitting by Expanded Access Application in IRB electronic application system.

5.6.3.1.3. The IRB is responsible for review of the treatment IDE in accordance with 21 CFR 812, 21 CFR 50, and 21 CFR 56.

6. References

6.1. 21 CFR 312.310

6.2. 21 CFR 312.315

6.1. 21 CFR 312.320

6.2. 21 CFR 312.310

6.3. Form FDA 3926

6.4. Expanded Access - Information for Physicians https://www.fda.gov/news-events/expanded-access/expanded-access-information-physicians

7. Previous Revisions: 12/2/12, 3/10/13, 12/5/21

8. Supersedes Policy: MHC_RP0128_" Emergency Use of Investigational Drugs and Devices".

MHC_RP0127 Investigational Drugs and Biologics Used in Clinical Research policy is now with corporate pharmacy. The number MHC_RP0127 is now assigned to policy Expanded Access of Investigational Drugs and Devices.

9. Approvals:

MHC Institutional Review Board acknowledgment: 7/20/12, 12/4/15

Signature on File *1/31/23*

Justin Klamerus, MD, MMM Date
Executive Vice President/Chief Medical Officer
Institutional Official of Research